DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/23/2011 has been entered.

Status of Claims

Claims 1 and 3 have been amended. Claims 2, 10 and 11 have been cancelled. Claims 1, 3-9 and 12-20 are pending, of which claims 5-7 and 14-20 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 3, 4, 8, 9, 12 and 13 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive for reasons set forth hereinbelow. In addition, the rejection under 35 U.S.C. 103(a) as over Odake (US 5,100,874) and Carpenter (6,656,448) has been reworded.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 4, 8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odake (US 5,100,874) in view of Carpenter (US 6,656,448).

Odake teaches peptide derivatives having specific inhibitory activity against collagenases (abstract). Abnormal overaction of collagenases is shown in processes of destruction and repair of tissues, and is observed for example in cases such as rheumatoid arthritis, periodontal diseases, etc. Inhibition of collagenases provides a useful means for treating such diseases (column 1, lines 1-22). New peptide compounds which selectively inhibit the action of collagenases derived from vertebrates without inhibiting other protease actions (i.e. exhibit an inhibitory action of high specificity), and which have low toxicity, improved metabolic rate are disclosed,

including peptidylhydroxamic acid derivatives of general formula X^1-X^2-X^3-X^4-NHOH (column 1, lines 45+). In particular, p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH is disclosed (claim 6). See also claim 1. Inhibitory activity against collagenases is disclosed in Tables 1 and 2.

Odake does not recite linking an imaging agent to the peptide derivative.

Carpenter discloses MRI contrast agents comprising one or more matrix metalloproteinase inhibiting targeting moieties attached to one or more paramagnetic metal ions, further comprising an optional linking moiety, L_n, between the targeting moieties and the paramagnetic metal ions. See column 5-6. The paramagnetic metal ions are present in the form of metal complexes or metal oxide particles (column 45, lines 24+). Iron is described as suitable paramagnetic metal. The pharmaceuticals have the formulae, $(Q)_d$--L_n—(C_h--X), $(Q)_d$--L_n --(C_h-X_1)$_{d'}$, **$(Q)_d$--L_n--(X_2)$_{d''}$,** and $(Q)_d$--L_n--(X_3), wherein Q represents a compound that inhibits a matrix metalloproteinase, d is 1-10, d'=1-100, L_n represents an optional linking group, C_h represents a metal chelator or bonding moiety, X represents a radioisotope, X_1 represents paramagnetic metal ion, X_2 represents a paramagnetic metal ion or heavy atom containing insoluble solid particle, d" is 1-100, and X_3 represents a surfactant microsphere of an echogenic gas (column 46, lines 1-28). Suitable MMP inhibitors include peptides, etc. (column 46). With regard to the targeting ligand, a functional group, such as --CONH--, OH, --COOH, or --SH, is necessary for a molecule to be an effective inhibitor of MMPs. This functional group is involved in the chelation of the active site zinc ion, and is commonly referred to as the zinc binding group or ZBG. The hydroxamate, for example, is a bidentate

ligand for zinc (column 46, lines 10-20). See also column 46-50, including succinyl hydroxamates and alanine hydroxamates as inhibitors. There are three key features of the pharmaceuticals that determine their efficacy: MMP selectivity, inhibitory potency, typically expressed as the K_i value, and the rate of clearance from the blood. Preferred pharmaceuticals of the present invention are comprised of inhibitors, Q, which exhibit selectivity for MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14 alone or in combination over the other MMPs. Most preferred are comprised of inhibitors, Q, which exhibit selectivity for MMP-2, MMP-9, or MMP-14 alone or in combination over the other MMPs. K_i values for the preferred pharmaceuticals of the present invention are <100 nM for one or more of MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14. K_i values for the most preferred pharmaceuticals of the present invention are <10 nM for one or more of MMP-2, MMP-9, or MMP-14.

A number of methods can be used to attach the MMP inhibitors, Q, to paramagnetic metal ion or heavy atom containing solid particles,X_2, by one of skill in the art of the surface modification of solid particles. In general, the targeting moiety Q or the combination $(Q)_d L_n$ is attached to a coupling group that react with a constituent of the surface of the solid particle. The coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

The imaging agents targeted to one or more MMP's would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes. These imaging agents,

containing a ligand directed at one or more MMP's (e.g. MMP-1, MMP-2, MMP-3, MMP-9), will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases (column 3, lines 51+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a diagnostic agent linked to the hydroxamic acid tetrapeptide derivatives of Odake when the teaching of Odake is taken in view of Carpenter. Odake teaches that his hydroxamic acid tetrapeptides, such as p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH (claim 6), have high inhibitory activity against collagenases. While Odake does not specifically recite linking the hydroxamic acid tetrapeptide collagenase inhibitors to a diagnostic agent (e.g. chelator or iron oxide for MRI), it is known in the art to provide MMP (collagenase) inhibitors linked with diagnostic agents, as taught by Carpenter, such as $(Q)_d$--L_n--$(X_2)_{d''}$, wherein Q represents a compound that inhibits a matrix metalloproteinase, L_n represents an optional linking group, and X_2 represents a paramagnetic metal ion containing insoluble solid particle (iron oxide). One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Carpenter teaches that linking MMP inhibitor to diagnostic agent provides the advantage of imaging cardiovascular pathologies associated with extracellular matrix degradation, such as atherosclerosis, heart failure, and restenosis in a patient involving: (1) administering a paramagnetic metallopharmaceutical of the present invention capable of localizing the loci of the cardiovascular pathology to a patient by injection or infusion; and (2) imaging the patient using magnetic resonance imaging (column 4, lines 55+).

Claims 1, 3, 4, 8, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Odake (US 5,100,874) in view of Carpenter (US 6,656,448), further in view of Portet (*J. Colloid Interfac. Sci.*, 2001, 238, p. 37-42).

The rejection over Odake in view of Carpenter is applied as above. It would have been further obvious to provide bis-phosphonate coating on iron oxide particles used as diagnostic moiety when the teachings of Odake and Carpenter are taken in view of Portet.

Portet discloses iron oxide nanoparticles as contrast agents in magnetic resonance imaging. Bisphosphonate coating on iron oxide provided the most stable coating in a wide range of pH, including neutrality, in comparison to carboxylates, sulfonates, etc.(abstract, page 42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide iron oxide particles coated with gem-bisphosphonate as the diagnostic moiety (paramagnetic metal ion oxide particle) in the compositions of Carpenter for use in targeted MRI imaging of MMP (collagenase) activity. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Portet teaches that bisphosphonate coated iron oxide particles are efficiently stabilized (page 42). In addition, Carpenter teaches that in synthesis, the coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

Response to Arguments

Applicant argues on pages 7-8 of the Response that Applicant disagrees with the Examiner's assessment that all collagenase inhibitors would have been considered interchangeable. As shown in Odake, inhibitors have different efficacy against different collagenases, and are different from another inhibitor (Odake col. 15-18, table 2). Accordingly, one of skill in the art would not blindly substitute a particular collagenase inhibitor taken from assessment of one collagenase, and apply it to a different physiological purpose for another collagenase as the Examiner has done.

This is not found to be persuasive. Carpenter teaches that a variety of MMP inhibitors are suitable for the purpose of conjugating to a diagnostic agent (column 5-11; 45-46). One of ordinary skill could have readily selected a specifically claimed collagenase inhibitor (e.g. claim 6) having specific inhibitory activity against collagenases (Table 2) for conjugation to diagnostic, as taught by Carpenter.

Applicant further argues on pages 8-9 of the Response that the Examiner has improperly attributed the characteristics of the MMP targeting entity of Carpenter to a peptide which has demonstrated a different activity in a different system, *i.e.,* the MMP inhibitor of Odake. The Examiner is not permitted to merely extract from cited references those teachings that support a conclusion of obviousness. The Examiner has provided no evidence that one of skill in the art would have any reasonable expectation that a peptide which has shown MMP inhibitory effect *in vitro* would be expected to have MMP targeting ability *in vivo,* or that the affinity or selectivity

for MMP would be sufficient for use as a diagnostic. In contrast, Lancelot *el al.* (of record) expressly compared whether the binding affinity *in vitro* (bound to the signal molecule), *in vivo* (not bound to the signal molecule) and *in vivo* would be the same for compound B *(See* Lancelot, page 426). Because Lancelot *et al.* specifically felt the need to test and report on each of these characteristics, a reasoned explanation would be that the authors did not expect these characteristics to be the same.

This is not found to be persuasive. The in vivo activity of FN-439 in vivo is known in the art at the time of the invention. See enclosed Kigasawa reference (*Jpn. J. Ophthalmol.*, 1995, 39(1), p. 35-42 (abstract)) that teaches that the effect of FN-439 in inhibiting corneal ulceration was investigated with alkali-burned rabbit corneas. FN-439 can block the active site of collagenase, and hydroxamic acid can chelate Zn^{2+} which is essential for collagenase activity. Corneal ulceration occurred in 5 of 9 control eyes, but in none of the nine eyes treated with FN-439. FN-439 may be useful for treating noninfectious corneal ulcers because of its potent activity and chemical and biologcial stability. Since it is established in the art that FN-439 has been used in vivo for act against collagenase in vivo, one of ordinary skill would have a reasonable expectation of achieving MMP targeting in vivo.

Applicant submits on pages 9-10 of the Response that the claims as currently pending are commensurate in scope with evidence of unexpected results, such that the claims recite a specific peptide. The evidence of record demonstrates that one of skill in the art would have expected to obtain either no MRI signal or only a non-MMP specific signal. Furthermore, looking at Odake (Table 2, cols. 15-18), the IC50 dosage for the

collagenase inhibitors reported therein were all in the micro-molar range. Thus, it would have been unexpected to obtain reliable data regarding binding and/or inhibition at the MMP concentrations in the nano-molar range as found in atherosclerotic tissue. Accordingly, because I) one of skill in the skill in the art would have not expected to detect MMP by MRI at nano-molar ranges, and 2) because looking at the inhibition data provided in Odake, one of skill in the art would not have expected the inhibitors to "work" in nano-molar ranges, Applicants maintain that one of skill in the art would not have expected the efficacy of the present invention as a diagnostic in view of Carpenter, Odake and Portet.

This is not found to be persuasive. First it is noted that Applicant's allegations of unexpected results are not commensurate in scope with the claimed invention. See MPEP 716.02(d). Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Claims were directed to a process for removing corrosion at "elevated temperatures" using a certain ion exchange resin (with the exception of claim 8 which recited a temperature in excess of 100C). Appellant demonstrated unexpected results via comparative tests with the prior art ion exchange resin at 110C and 130C. The court affirmed the rejection of claims 1-7 and 9-10 because the term "elevated temperatures" encompassed temperatures as low as 60C

where the prior art ion exchange resin was known to perform well. The rejection of claim 8, directed to a temperature in excess of 100C, was reversed.). See also *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the *prima facie* case because experiments limited to sodium were not commensurate in scope with the claims.). In the instant case, it is noted that Applicant asserts on page 9 of the Response that "one of skill would have expected to obtain either no MRI signal or only a non-MMP specific signal" and that "this very weak quantity could normally not have been detected by MRI with the relaxivity level of the compound used in the present invention (about 5 mM-1 Gd-1s-1)," however the claims are drawn to any signal entity for medical imaging, which may be inclusive of e.g. microbubbles for ultrasound imaging, chelating agent for MRI imaging, radionuclide for scintigraphic imaging, fluorescent dye for optical imaging, etc. Applicant's specification at published paragraph 0009 recites that "the sensitivity of MRI in vivo is relatively low compared to scintigraphic imaging techniques, for instance," which provides a teaching that different imaging techniques have different sensitivity. Accordingly, allegation of unexpected results with regard to MRI imaging is not commensurate in scope with the claims which may include any medical imaging entity.

It is further noted that the arguments of counsel cannot take the place of evidence in the record. See MPEP 2145. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration. Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. In the instant case, only attorney arguments have been presented to support the argument that "one of skill in the art would have expected to obtain no MRI signal or only a non-MMP specific signal," based upon - the M“P concentration in targeted atherosclerotic tissue was about 50 nM and -this very weak quantity could normally not have been detected with the relaxivity level of the compund used in the present invention (about 5 mM-1 Gd-1 s-1); indeed acccording to common knowledge in the MRI field at the time the application was filed, the sensitivity of MRI should not have been able to allow the imaging of a biological target at a concentration of less than about 10 µM to 1 mM.” In the instant case, an assertion of what seems to follow from common experience amounts to attorney argument. Furthermore, Carpenter teaches using imaging agents targeted to

one or more MMP's would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, *atherosclerosis* and other degradative disease processes. These imaging agents, containing a ligand directed at one or more MMP's (e.g. MMP-1, MMP-2, MMP-3, MMP-9), will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases. The MMP targeting ligand could be bound to a single or multiple chelator moieties for attachment of one or more paramagnetic metal atoms, which would cause a local change in magnetic properties, such as relaxivity or susceptibility, at the site of tissue damage, which could then be imaged with magnetic resonance imaging systems. Suitable chelators include DOTA. Accordingly, there was at least some expectation in the art that MMP targeting agents conjugated to DOTA chelating paramagnetic ion would be capable of in vivo imaging of atherosclerosis.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Wednesday 9 AM-5 PM and telework Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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